PreventionPOST

June 2000
VOLUME 2/ISSUE 1

NEWSLETTER OF THE NCI DIVISION OF CANCER PREVENTION

NATIONAL CANCER INSTITUTE

IN THIS ISSUE

From the Top

BARRY KRAMER
Deputy Director, DCP

The core mission of the Division of Cancer Prevention (DCP) is to conduct and support research to improve the health of the public by decreasing the incidence, mortality, and morbidity of cancer. Throughout medical history, many of the improvements in health have derived from advances in public health science and prevention. DCP continues in that tradition. Each component of our Division is an integrated part of the whole, starting with basic discoveries in nutrition, chemoprevention, and molecular markers. The goal is application to prevention, early detection, and survivorship; and the most efficient and definitive test of the true worth of the applications at the population level is the large scale clinical trial. We have championed definitive testing of discoveries from a broad range of disciplines such as epidemiology, molecular biology, medical oncology, and clinical diagnostics in definitive prevention and screening trials. The Breast Cancer Prevention Trial represented the first time in history that a medical intervention was definitively shown to decrease the incidence of a common cancer. In that sense, our Division has already written an important chapter in medical history. And much more history remains to be written by us. Efforts continue for a number of very high profile diseases that afflict Americans: cancers of the colon, lung, prostate, breast, ovary, cervix, and others. Our efforts are important to the public, which places strong emphasis on primary prevention of cancer. Some of our pioneering studies are described in this issue of the **PreventionPOST**. They are palpable evidence of what our dedicated staff can accomplish and of what the future can hold. ■

The Trials of DCP

PAMELA MARCUS

Our business in DCP is prevention—cancer prevention to be exact. When we think of prevention, we think about ways of frustrating cancer, of putting obstacles in its path. But how do we know what works and what doesn't work? That's where the *clinical* trials of DCP come into play. Clinical trials allow for rigorous scientific evaluation of medical interventions, including chemopreventive agents, screening modalities, and cancer treatment regimens. Because DCP is an extramural division, we administer a plethora of trials, some small and others quite large. Clinical trials are among the most important cancer prevention research being conducted in the world today.

DCP's trials often focus on primary prevention, i.e., strategies for reducing the incidence of disease. Chemoprevention – administration of a pharmaceutical agent to reduce cancer risk – is a major focus. One of DCP's historically important endeavors, the Breast Cancer Prevention Trial (BCPT), examined whether daily administration of 20 milligrams (mg) of tamoxifen (brand name, Novaldex®) for 5 years reduced breast cancer incidence in women at high risk of the disease. BCPT began in 1992 and randomized, in a double-blinded man-

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Trials of DCP continued from page 1

ner, over 13,000 women to either tamoxifen or placebo. In mid-1998, investigators reported a significant 49% decrease in breast cancer incidence for the group taking tamoxifen, and in October of that year, the Food and Drug Administration (FDA) approved tamoxifen for prevention of breast cancer in high-risk women. Tamoxifen remains the only drug approved by the FDA for reduction of risk of breast cancer in high-risk women.

Another pharmaceutical, raloxifene (brand name, Evista®), currently is challenging tamoxifen in the Study of Tamoxifen and Raloxifene (STAR). Raloxifene is a potentially promising breast cancer chemopreventive agent, having been observed to reduce breast cancer incidence by 76% in a clinical trial designed to assess its usefulness in the prevention and treatment of osteoporosis. STAR opened enrollment in May, 1999 and will randomize, in a double-blinded manner, around 22,000 post-menopausal women to either 20 mg of tamoxifen daily or 60 mg of raloxifene daily for 5 years. In addition to assessing whether raloxifene does as good a job as tamoxifen at reducing breast cancer incidence, a major focus of STAR is to compare the long-term safety of the agents. Tamoxifen is known to, and raloxifene may possibly, increase risk of deep vein thromboses and pulmonary embolisms (blood clots); both side effects can be fatal. Tamoxifen also is known to increase the risk of endometrial cancer.

Prostate cancer chemoprevention also is under study in DCP. The Prostate Cancer Prevention Trial (PCPT) is currently examining whether finasteride (brand name, Proscar®) can reduce prostate cancer incidence. Finasteride was approved by the FDA in 1993 for the treatment of benign prostatic hyperplasia (BPH), and although never previously used to prevent cancer, the drug reduces levels of dihydrotestosterone, a male hormone believed to be involved in prostate cancer development. PCPT began in 1993, closed enrollment in 1996, and randomized 18,882 healthy men aged 55 and older to receive either 5 mg of finasteride or placebo daily for 7 years in a double-blinded manner. The PCPT is in full swing right now, with the first enrollees scheduled to finish their drug regimens in October of this year. Final results are expected towards the end of 2003 or in early 2004.

Another trial of prostate cancer prevention is in its start-up phase. The Selenium and Vitamin E Clinical Trial (SELECT) will randomize 32,400 healthy middle-aged and elderly men to one of four daily supplement regimens. SELECT will use a factorial design, with participants receiving one of the following regimens: 200 micrograms (µg) of selenium, 400 mg of vitamin E, 200 µg of selenium and 400 mg of vitamin E, or only placebo. Both selenium and vitamin E have shown promise as chemopreventive agents for prostate cancer in clinical trials designed to assess the effects of those agents on other cancers. A Request for Applications (RFA) was issued in 1999; study center applications were due this past February. SELECT is expected to randomize its first participant in the fall of 2000.

Prevention also can be accomplished through the use of mass screening programs. The goal of these programs is to reduce the death toll from cancer by identifying cancerous lesions earlier, at a time when tumors are asymptomatic and

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HISTORY OF CANCER PREVENTION

Pioneers of Progress: Major Greenwood, Austin Bradford Hill, and the Development of the Randomized Clinical Trial (1900-1950)

DOUGLAS L. WEED

Major Greenwood
(Courtesy of the National Library of Medicine)

The first half of the Twentieth Century was a time of remarkable progress in medicine and in statistics. The discovery of antibiotics effective against syphilis, puerperal sepsis, pneumonia, malaria, and tuberculosis changed the way medicine was practiced and improved the health of many communities. During this same period, the methods used to assess the efficacy of medical interventions evolved from relatively simple deterministic models to the probabilistic models so familiar today. Inferences from clinical studies on single-arm series of patients were enhanced by the use of historical controls and by efforts to make controls as similar as possible to treated cases. Randomization came into vogue relatively late in this era. Two small (and null) randomized trials, in 1931 and 1943, went virtually unnoticed. But in 1948, a successful trial of streptomycin for pulmonary tuberculosis was published in the British Medical Journal by the Medical Research Council (MRC). Austin Bradford (Tony) Hill (see photo page 3) was Director of the Statistical Research Unit of the MRC at the time, as well as Professor of Statistics and Epidemiology at the London School of Hygiene and Tropical Medicine, a position recently vacated by Hill's mentor, Major Greenwood (see photo left). These two pioneers of statistics and epidemiologic methodology laid down the foundation for what is now considered a scientific paradigm: the randomized clinical trial.

Greenwood trained as a physician and undertook a research career under the tutelage of Leonard Hill (Austin Bradford Hill's

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Project Teams

JENNIFER FLACH

As DCP's matrix-based organization evolves, project teams (a.k.a. "eggs") are growing in number and scope. Project team members join together to tackle specific tasks in the Division. Projects suitable for team work include the following: planning research initiatives, coordinating workshops to address particular topics, and addressing administrative issues important to the Division's mission. Project teams also provide a mechanism for DCP staff to collaborate with outsiders who have an interest in the Division's activities. Staff from other NCI Divisions, DCP advisory groups, representatives from other Federal agencies, extramural researchers, and others are often invited to participate in project teams.

If are you reading this article, you may know about the DCP Newsletter Project Team, but what about the others? (See list of project teams in side box.)

Selected Project Teams (Team Leaders)

Cancer Genome Anatomy Project - CGAP (Barbara Dunn)
EGGS Database (Karen Johnson)
Prevention of Languishing Studies (Jaye Viner and Rose Mary Padberg)
HPV Vaccine (Terri Cornelison)
Assessment of Spiral CT (John Gohagan)
DCP Newsletter (Doug Weed)
Ovarian Cancer Prevention (Karen Johnson)
Molecular Targets for Dietary Prevention of Prostate Cancer (Carolyn Clifford)
Molecular Signatures of Infectious Agents (Sudhir Srivastava)
Single Nucleotide Polymorphisms (Iqbal Ali)
Non-scientific Staff (Felicia Carr)
Protocol Review Project (Lori Minasian)

EGGS Database

Creating a project team involves obtaining the sponsorship of a Coordinating Unit member, recruiting members, and submitting a proposal to the Coordinating Unit for approval. The process includes completing the Project Team/Capsule Concept Proposal form. Karen Johnson leads a team with the task of developing EGGS, the project team database. This database will manage information about Division project teams. When it is completed, DCP staff will be able to access the database to find out what's happening on the project teams.

Assessment of Spiral CT

DCP has formed a project team to evaluate the feasibility of conducting a randomized clinical trial (RCT) of low-dose spiral (helical) computed tomography (CT) as a screening modality for lung cancer. Currently no lung cancer screening modality is recommended by any organization. However, chest x-ray is being evaluated in the PLCO trial. During the last decade, progress in diagnostic imaging established high-resolution computed tomography (HRCT) as the standard of practice for assessing lung abnormalities observed on chest x-ray. Low-dose spiral CT as a technolog-

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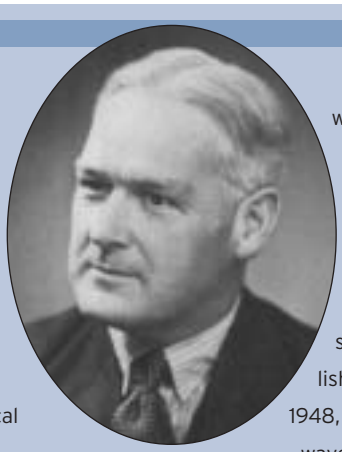
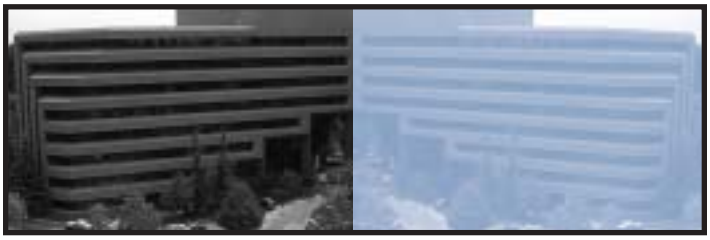
Pioneers of Progress continued from page 2

father). He learned mathematical statistics from Karl Pearson at University College, London. His research interests were broad by today's standards, ranging from vital statistics to experimental epidemiology (in which epidemics were observed in mouse populations under controlled conditions). He studied industrial accidents, nutritional deficiencies, the physiologic effects of compressed air, and theoretical statistics. On the subject of cancer, Greenwood wrote in a 1935 textbook that statistical and epidemiological methods had reached no clear-cut conclusion of general etiologic importance. He was convinced nevertheless that cancer prevention was a likely reality. He described cancer mortality differences in different social classes and for cancers of the "upper part of the alimentary canal." Greenwood proposed that some as-yet-unknown manipulable exposure was responsible for the differences observed. We recognize today that smoking may have been the culprit, as Greenwood's student, Tony Hill, would later study in a large cohort of British physicians, a study he collaborated on with Richard Doll. Hill intended to study medicine but gave it up after a long convalescence for tuberculosis acquired in World War I. He studied economics, then statistics (also under Karl Pearson) and worked with Major Greenwood at the MRC. His series of papers in Lancet (1937) were eventually published as one of the first textbooks of medical statistics. In 1948, and for several years following, Hill rode a remarkable wave of interest in randomized trials, publishing papers on their conduct, ethics, and statistical analysis. Hill's contribution to the design and conduct of randomized clinical trials was judged by some to be as valuable as the discovery of penicillin. Today, the randomized trial remains our methodologic gold standard, thanks in great measure to the remarkable work of Major Greenwood (1880-1949) and Austin Bradford Hill (1897-1991). ■



Sir Austin Bradford Hill



DCP home base: Executive Plaza

ical refinement of spiral CT utilizes the simultaneous smooth, continuous movements of a rotating x-ray tube and horizontally moving x-ray table to produce views of the lung. This technology permits continuous rapid acquisition of images of multiple thin sections of an entire chest in a single breath hold, typically about 15 seconds. The Lancet published the baseline results from the Early Lung Cancer Action Project (ELCAP), a study that explores the ability of low-dose spiral CT to detect lung cancer lesions. A randomized control trial is needed to assess the mortality impact of lung cancer screening by spiral CT. The Spiral CT Assessment Project Team includes members from the EDRG, BRG and OD of the Division of Cancer Prevention.

Cancer Genome Anatomy Project (CGAP)

The CGAP Project Team is tapping into the resources of the NIH Cancer Genome Anatomy Project. The CGAP is an interdisciplinary initiative for the development of informatics and scientific tools needed to decode the molecular anatomy of the cancer cell. The focus of the CGAP project team is to investigate the differential expression of genes in precancerous versus normal (or at-risk normal appearing) tissue in human and animal models. Results of these investigations will provide insight into the mechanisms of carcinogensis and be used in the development of new chemopreventive agents. Barbara Dunn of the Basic Prevention Science Research Group leads the team, which includes members from a variety of DCP research groups as well as external members involved in the CGAP. The team plans to implement pilot projects that will lead to larger research endeavors such as Program Announcements and Requests for Applications.

HPV Vaccine

The Human Papilloma Virus (HPV) Vaccine Project Team was created to implement recommendations resulting from a September 1998 meeting on cervical cancer and HPV vaccines. HPV is associated with the development of up to 95% of cervical cancers. Prophylactic vaccines for HPV have shown feasibility in animal models, leading to investigations in humans. The team is reviewing the efficacy endpoints for therapeutic/preventive vaccines for HPV, working with clinical trials cooperative groups to identify potential study populations, working with researchers in DCEG to plan a prevention trial of an HPV vaccine in Costa Rica, and exploring collaborations with industry. DCTD, DCEG, and FDA are also represented on the project team. Terri Cornelison, Breast and Gynecologic Cancers Research Group, is the team leader.

Nonscientific Staff

The Nonscientific Staff Project Team was one of the earliest project teams started in the Division. This team was created as a way for nonscientific staff to be more involved in planning and coordination of administrative support functions of the Division, such as preparing travel, training new administrative staff, and meeting planning. Felicia Carr, the team leader, explained that the team wants to "be out there, to be helpful to scientific staff." In particular, the team offers its expertise to research groups needing help in the reorganization.

Protocol Review

One of the primary functions of the Division of Cancer Prevention is the scientific, regulatory, and administrative review of clinical protocols and concepts it sponsors. In the past, the Community Oncology and Prevention Trials Research Group and the former Chemoprevention Branch conducted separate protocol reviews. After DCP's reorganization, the work of the Chemprevention Branch was spread across several research groups and it became apparent that a centralized review function was needed. In June of 1999, the Protocol Review Process Project Team was formed to explore existing procedures for reviewing clinical protocols and make recommendations for coordinating and streamlining review efforts. Linda Parreco was hired to head a centralized Protocol Information Office (PIO) for DCP, in the Office of the Associate Director for Clinical Research. She credits the Protocol Review Project Team for laying much of the groundwork for the creation of the PIO. "The vision for the PIO was to create a single process whereby Phase I-III clinical research concepts and protocols, regardless of funding sources, are reviewed in a centralized process," said Linda. "We see the PIO development process as a tangible growth opportunity for the Division. It forces us to have a clear vision of what research we want, what we want it to look like, and how we will evaluate it," she added. ■

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Congratulations!

TERRI L. CORNELISON

The Individual Spotlight goes to Karen Johnson, newly appointed Chief of the Breast and Gynecologic Cancer Research Group, and Sudhir Srivastava, newly appointed Chief of the Cancer Biomarkers Research Group.

Karen Johnson

Karen Johnson is a medical oncologist and Maryland native. She received her first diploma from Miss Welch's Jack and Jill Kindergarten, Chestertown, Maryland, and "was so pleased with that diploma that I kept trying to get more". She completed a Ph.D. in inorganic chemistry at the University of Delaware, was a medical student at Jefferson Medical College, Philadelphia, resident and oncology fellow at Georgetown University Hospital, and received her M.P.H. from The Johns Hopkins University. Dr. Johnson's areas of interest are breast and ovarian cancers.

Who were your most influential teachers? My parents. They were both school teachers, and they started my instruction early.
What world event had a major effect on your life? The assassination of John F. Kennedy, because it confirmed fatalism.
How do you relax? Reading fiction and antiquing.
What is your favorite play? *She Stoops to Conquer*, by Oliver Goldsmith (1728-1774), because it makes you laugh.
What is your favorite book? *The End of the Pier,* by Martha Grimes. It is well constructed and poignant in understanding life.
Who is your favorite author? Thomas Hardy.
What is your favorite sound? A child's voice.
What is your favorite vegetable? Garden tomatoes.
What is your favorite sport? As a participant, tennis; as a spectator, ice skating.
What is your greatest accomplishment to date? Just surviving, hopefully with grace; and not yet having become an embarrassment to my young nieces aged 7 to 15!

Sudhir Srivastava, who has been at the NCI since 1987, was born in Azamgarn, India, and immigrated to the United States in 1977, after obtaining a Ph.D. at age 23 from Banaras Hindu University in biological science. In the U.S., he obtained two masters' degrees: one in computer science from Virginia Commonwealth University (VCU) and one in public health from The Johns Hopkins University. Dr. Srivastava taught in the Department of Physiology and Biophysics at VCU for five years before his interest in prevention research brought him to the NCI. Dr. Srivastava is the youngest, non-clinical and first Asian-American elected to the prestigious American Joint Committee on Cancer. His specific research interest is molecular detection and screening of cancer.

Sudhir Srivastava

What has had the most effect on your work? Family members afflicted with cancer. My cousin has gallbladder cancer, and my aunt had cervical cancer.
What event had the most effect on your life? My mother's death. I shared my glories and agonies with her. I was so inspired by her strength and dignity through her own struggles that I was able to carry on.
What is your best advice for young investigators in cancer prevention medicine? Be persistent and dedicated to prevention research, as this is still an evolving field and answers may not be apparent soon.
What are your favorite books, and why? Biographies of President John F. Kennedy and Mahatma Gandhi (Mohan Das Karam Chand Gandhi). Both are inspirational with forward-looking ideas.
What is your favorite sound? Flowing river.
What is your favorite vegetable? Okra.
What do you hate the most? Waiting.
What place have you never been to that you would like to visit? Africa. I would like to go on a Safari.
What is your proudest moment? Succeeding in my belief.
What is your greatest accomplishment to date? The successful launching of the Early Detection Research Network. ■

At the Forefront of Training

SUSAN WINER

The Cancer Prevention Fellowship Program (CPFP) has been busy. In November, twenty-eight applicants were interviewed for the Fellowship Program, Class of 2000. This is a new record! Fifteen offers were extended and 15 were accepted. During the three day interviewing process, we invited three former Fellows to give a lecture as part of the ongoing DCP Colloquia series: Karen Kafadar, PhD (University of Colorado at Denver), Florence Houn, MD, MPH (FDA), and Ann Coleman, PhD (University of Arkansas for Medical Science).

The new class of Fellows includes:

Erik Augustson, PhD, University of Alabama; **Alexis B. Bakos, PhD,** Johns Hopkins University School of Nursing; **Jagjit S. Gill, PhD,** Mayo Graduate School; **Elizabeth Jones, MD,** Clinical Center, NIH; **La Creis Kidd, PhD,** Johns Hopkins University School of Public Health; **Kerri McGowan Lowrey, JD,** Division of Cancer Control and Population Sciences, NCI; **Theodore Marcy, MD,** University of Vermont College of Medicine; **Leah Mechanic, PhD,** University of North Carolina at Chapel Hill; **Pauline Mysliwiec, MD,** Indian Health Service/Phoenix Indian Medical Center; **Dina Paltoo, PhD,** Morgan State University; **Mark Parascandola, PhD,** Clinical Center, NIH; **Heather Poetschke, PhD,** University of Texas, MD Anderson Cancer Center; **Susan Steck, PhD,** MPH, University of North Carolina at Chapel Hill; **Susan Thomas, PhD,** Indiana University; **Janet Tooze, PhD,** University of Colorado Health Sciences Center; and **Maja Zecevic, PhD,** University of Virginia Cancer Center. Nearly all of these new Fellows will first be obtaining Masters of Public Health (MPH) degrees at schools of public health around the country.

Just completing their MPH's are 8 second year Fellows who will be joining us at the NCI in June. They will begin their training by attending summer prevention courses and after will include work with an approved NCI preceptor. These fellows include:

David Berrigan, PhD, MPH (exp.), University of California, Berkeley

Philip Castle, PhD, MPH (exp.) Johns Hopkins University

Graça Dores, MD, MPH (exp.) University of Alabama at Brimingham

Mollie Howerton, PhD, MPH (exp.), Johns Hopkins University

Claudine Kavanaugh, PhD, MPH (exp.), Johns Hopkins University

Jackie Lavigne, PhD, MPH (exp.), Johns Hopkins University

Janet Newburgh shows Charisee Lamar and Pam Mink a typical delivery of grant appications at CSR.

Volker Mai, PhD, MPH (exp.), Harvard University

Pothur Srinivas, PhD, MPH (exp.), Johns Hopkins University

Also joining this group are two new Fellows who previously received their MPH's: Elizabeth Jones, MD, PhD (exp.) Johns Hopkins University and Susan Steck, PhD, MPH University of North Carolina, Chapel Hill.

New Course in Grants and Grantswriting

In January, as part of the growth of the Fellowship Program, a new course was offered, Grants and Grantsmanship Workshop. This new course was created to teach our Fellows the ins and outs of grant writing. For those Fellows who plan to return to academia, grantsmanship is an important career development tool. Guest lecturers for the course were current NCI grantees Shine Chang,

Christian Abnet, Steve Hursting, Rachel Stolzenberg-Solomon, Beth Dixon, Heng Xie, Lisa Colbert and Christine Sweeney examine examine applications as Dr. Newburgh explains the assignment.

PhD and Maureen Goode, PhD from the University of Texas, M.D. Anderson Cancer Center and Ginger Krawiec, MPA from the American Cancer Society headquarters in Atlanta, Georgia. Also presenting at the course were Sherry Mills, MD, MPH, Suresh Mohla, MD, PhD, and Lisa Begg, PhD, all from the NCI. Each Fellow was asked to prepare a 2-page grant. Mac Stiles, DDS, PhD, MPH, of NIH's Center for Scientific Review, NIH, held a mock study section for the grant applications. The course was a great success and several of the Fellows suggested that a grant writing club be formed. A volunteer writing club that meets twice a month has been set up. Currently, 8 Fellows are in the club. Steve Hursting is the mentor for this group.

The group looks at the shelves soon to contain applications assigned to an institute for review.

As part of the course, Fellows visited the Center for Scientific Review (CSR). Dr. Janet Newburgh, Referral Officer, Center for Scientific Review, gave the Fellows a first-class tour of the facilities from the receiving dock at the back door of the building to the room that codes and assigns each and every submitted grant. The Center for Scientific Review receives all NIH grant applications, and then codes and distributes each grant to the appropriate Institute and Division.

Summer Curriculum

In July, we start our summer short courses in cancer prevention. This year several changes have taken place. First, we have a new name for this activity: the NCI Summer Curriculum in Cancer Prevention. We also have divided the course into 2 parts. The first part, Principles and Practice in Cancer Prevention and Control, will be held from July 5 to August 4. The second part, Molecular Prevention, will be held from August 7 to August 11. Also, we have new topics and new lecturers. In addition, we have added a special feature to this summer activity—the First Annual Advances in Cancer Prevention Lecture. This summer's speaker is Bernard Levin, MD, from The University of Texas, M.D. Anderson Cancer Center. This lecture will be held in the Lister Hill auditorium (NIH main campus), on Thursday August 3rd at 3:00 p.m. All are invited to attend.

Our widely popular summer course attracts a variety of attendees. Every summer the NCI's Office of International Affairs sponsors a number of interested clinicians and researchers from developing countries. These attendees come primarily from Asia, Eastern Europe, South America, and Africa. Our 2nd year Fellows and other interested people complete the audience. If you would like to attend all or any part of these courses, please contact our office at 301-496-8640 and we will happily to assist you.

Interview with a former Fellow

Diana Jeffery

In November, 1999, one of our graduates, Diana Jeffery, PhD, joined the NCI as a Health Scientist Administrator/ Program Director in the Division of Cancer Control and Population and Sciences. She will administer 30-40 grants, mainly R01s. Diana was a Fellow from 1986-88, back when the Fellowship Program was referred to as the Cancer Control Science Associates Program. The program is now called the Cancer Prevention Fellowship Program.

When you left the NCI, where did you go?

I left the Program and went to the Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center in New York. Then in 1989, I went to the Nursing Research Center, Vanderbilt University School of Nursing as an Assistant Professor and Assistant Director. At the same time I was the Associate Director of Nursing, Nursing Research, Veterans Hospital in Nashville, Tennessee. In 1995, I joined the Hawaii State Health Department in the Epidemiology Department. Taking on the duties of a Clinical Psychologist in 1998, I worked at the Kapiolani Women's Center in Honolulu.

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DCP Newsletter Project Team

EDITORIAL GROUP:
Doug Weed (Editor-in-Chief),
Pamela Marcus, Judy Smith, Dee Sullivan

GRAPHIC ARTS GROUP:
Terri Cornelison, Jennifer Flach

DISTRIBUTION & INTERNET GROUP:
Ron Lubet, Michelle Nestorio, Susan Winer

CONTRACT & LIAISON GROUP:
Don Henson, Pamela Marcus

SPECIAL THANKS

Special thanks go to Cancer Prevention Fellow Graça Dores, MD, MPH (exp.), our resident cartoonist. Dr. Dores was the Director, Special Hematology/Oncology Laboratory at the Memorial Hospital in Providence, Rhode Island before her acceptance into the NCI Fellowship Program. Graça went to the University of Alabama in Birmingham for her MPH. She will be relocating to the DC area to begin the second year of her Fellowship at the NCI.

Also, very special thanks go to Linda Bremmerman and Eric Graves for their enthusiasm and tireless effort in producing the first edition of **PreventionPOST**. Please welcome the newest member of the team, Judy Smith, RN, MSN, AOCN. Judy is part of the Lung and Upper Aerodigestive Cancer Research Group.

DCP Winter Bash!

PAMELA MARCUS

From trail mix to fresh asparagus to tiny toast, there was something for everyone at this year's DCP winter party. Held on the afternoon of Friday, January 21st at the home of DCP's very own Dave Levin, more than 60 DCP'ers stopped by to munch, mingle, and catch up with their colleagues. The Biometry Research Group, charged with organizing the party, did a fantastic job, due in particular to the hard work of Vance Berger, Christine Donati, Richard Fagerstrom, Jenny Gaegler, Grant Izmirlian, Dave Levin, and Pam Marcus.

In between the socializing, guests enjoyed a wide variety of snacks. On the menu were nutritious finger foods, including plenty of those fruits and veggies to help everyone reach that 5-a-day goal! Cheeses were available, as were tasty dips, pasta salads, and hot apple cider. For those looking to cheat on their diets, cookies and chips also could be found. It was a party, after all!

Live entertainment was provided by DCP's Grant Izmirlian and his friend Russell Sledge. Grant, on the sax, and Russell, on the bass, jammed on jazz classics, including "Blue in Green," a Miles Davis classic, and "Donna Lee," made famous by Charlie Parker. After Russell's departure, Grant switched over to the piano, entertaining guests with his rendition of Scott Joplin's Maple Leaf Rag and Bach's Goldberg Variations.

Door prizes also were a part of this year's DCP party. Harriet Greenwald, in a very fair and high-tech manner, pulled names from a glass fish bowl. Barbara Dunn of the Basic Prevention Science Research Group won a gift certificate to Giant, and Gary Kelloff of the Chemopreventive Agent Development Group won a potpourri mat. The other prizes—a chocolate rose and a gift certificate to Fresh Fields—went to Don Corle and Jenny Gaegler, both of Biometry. Questions were raised regarding the preponderance of winners from the research group responsible for organizing the party, but Biometry statisticians, as to be expected, were quick to attribute it to chance. ■

Barry Kramer, Peter Greenwald, Karen Johnson, Richard Fagerstrom, and Phil Prorok share a laugh while munching and drinking cider.

Peter Greenwald, Mary Lou Carter, Barbara Redding and Susan Winer.

Socializing in the sun room, from left to right: Linda Gray, Judy Binstock, Ned Englund, Gloria Rasband, Mukesh Verma, Andrew Hruszkewycz, Vance Berger, Peter Greenwald.

Carolyn Clifford and Leslie Ford chat.

Temugen Wallace enjoys fresh steamed asparagus.

Winter Bash!

Dave Levin shows Ping Hu the merits of his kitchen appliances.

Victor Kipnis, Rose Mary Padberg, Shannon Brandon, and Barry Portnoy enjoy the fine fare and good company.

Cancer Prevention Fellowhsip Program continued from page 7

What brought you back to the NCI?

I was not particularly happy with managed care and decided to look around and I saw the opening advertised in the American Psychological Association's magazine, the Monitor. This is just what I wanted to do; I sent in my application, interviewed, and got the job.

What changes have you noticed in the Fellowship Program?

A lot of changes have been made. In the beginning, only MDs could get an MPH degree and Fellows had a GS rating. You had to have your PhD for two years before applying to the Program. There were 3 people in the class and we had 6 months of intense classroom instruction. When the course was completed, we were heavily recruited by all of the Divisions. I did site visits, went to grant reviews, and had homework every night. Our program leader, Dr. David Poskanzer, was in charge of the training and the branch and almost all of our lecturers were from NCI.

What do you see in the future for cancer prevention?

I would like to see more behavioral work and more research done on survivors, especially in under-served populations including the elderly. The quality of care for the elderly with cancer is a special concern, as is public policy and the HMOs.

Recruitment

The Cancer Prevention Fellowship Program has recently begun a major recruitment effort for the Fellowship Program. In early March, Susan Winer set up a booth at the Johns Hopkins University School of Public Health's Marketplace 2000 Career Fair. Former Hopkins graduates Rita Misra, PhD, MPH and Christine Sweeney, PhD, MPH, helped to answer questions. Our current Hopkins students also stopped by. Later in the month, Susan set up a recruitment exhibit for the Fellowship Program at the Prevention 2000 meeting held in Atlanta. Over 500 people attended the meeting. The NCI has a large display booth that is on display at many of the large research meetings. Our brochures and information on the Fellowship Program are prominently displayed.

About the Fellows

Many of our Fellows continue their careers by joining the NIH. Joining the NCI recently are Karen Woodson, PhD, MPH and Luke Ratnasinghe, PhD, MPH in the Division of Clinical Sciences. Samir Sauma, PhD, MPH is now working in the Office of Science Opportunity, Office of the Director. Maria T. Canto, DDS, MPH recently joined the National Institute of Dental and Craniofacial Research. Congratulations and best wishes for their continued success!

Special congratulations go to three former Fellows, Rosalind Breslow, PhD, MPH; Pamela Marcus, MS, PhD; and Stephen D. Hursting, PhD, MPH, who presented at the Plenary Session of the American Society of Preventive Oncology meeting, held in Bethesda, MD, on March 5 through 7. Their papers were among the top 5 abstracts submitted. Also presenting an abstract was current Fellow, Rachel Stolzenberg-Solomon, PhD. Her abstract was selected as one of the top 16 submitted. The poster sessions were well represented by both current and former Fellows. Current Fellows Lisa Colbert, PhD, MPH and Kathy Radimer, PhD, MPH had posters, as did two former Fellows, Sharada Shankar, PhD, MPH and Ann Coleman, PhD. who received an Honorable mention in the Best Poster award. In addition to presenting at the Plenary Session, Steve Hursting also had a poster on display.

At the 1999 ASPO meeting in Houston, TX, two of the five plenary talks were from former Fellows, Karen Woodson, PhD, MPH and Steve Hursting, PhD, MPH. Dr. Hursting, the Deputy Director of the Cancer Prevention Fellowship Program, was also a plenary speaker at the 1998 ASPO meeting.

All in all, our Fellows have done a terrific job at the ASPO meetings!

Congratulations go to Kevin and Kimberly Knopf on the birth of their second child, a daughter, Sarah Bingham. Sarah is welcomed to the family by her brother, Nathaniel.

Did you know that Christian Abnet, PhD, MPH, has a license to perform marriages? When asked what his motivation was for applying for the license, Christian said that he did it to be able to legally perform a friend's wedding. ■

Effects of the COX-2 Inhibitor Celecoxib in Patients with Familial Adenomatous Polyposis: Anatomy of A Prevention Trial

RON LUBET

The headline in the January 17, 2000 Science section of the New York Times read "Serendipity And Hope In Our War on Cancer." The major impetus for the article was COX-2, a possible pharmaceutical agent for cancer prevention/treatment, and a recently completed Phase II/III clinical trial of the drug. This trial, which was funded and heavily developed by the Division of Cancer Prevention, examined the efficacy of the COX-2 inhibitor Celecoxib on regression of existing polyps in individuals with familial adenomatous polyposis (FAP). The trial led to FDA approval of Celecoxib for individuals with FAP and directly reflects major efforts by the Gastrointestinal and Other Cancers Research Group (GOCRG) and the Chemoprevention Agent Development Research Group (CADRG). In totality, it is a collaborative effort based on interactions between GOCRG, CADRG, clinicians at M.D. Anderson (Houston, TX) and St. Marks (London, UK), and G. D. Searle, a pharmaceutical firm. As with any trial, this trial practically dictated the need for one or two primary spokespersons; nevertheless, the Celecoxib trial actually represents the efforts, knowledge, and eccentricities of a far wider range of individuals including the COX-2 developmental people at Searle, clinical and preclinical people at DCP, the clinicians at the two primary sites and finally, and perhaps most importantly, the patients who enrolled in the trial.

What the Trial Showed

Seventy-seven patients with FAP, a genetic syndrome associated with germ line mutations in the APC gene, were randomized to receive placebo or Celecoxib for six months. FAP individuals typically develop hundreds of adenomas in the colon beginning in their mid to late teens. Thus, each participant in the study had multiple existing polyps at the initiation of the study. The study endpoints included determining the effects of Celecoxib on number and size of identified polyps and an overall assessment of its efficacy based on blinded review of videotaped endoscopies by a panel of five experts. Celecoxib caused a dose-dependent reduction in total polyp number, with an approximate 30% reduction for the highest dose. Furthermore, the expert panel assessed a significant improvement in overall disease for individuals receiving the highest dose of Celecoxib, as compared with a

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DCP Websites

DONALD E. HENSON

Want to learn about the research activities in DCP? Then check out its website! The DCP Homepage (http://dcp.nci.nih.gov) contains links to key division activities, function statements, e-mail addresses, Division reports, and other useful information. A chart of the new organizational structure is even available. Designed as an image map, the chart actually simplifies finding websites. A click on the name of any organ based or foundation research group will bring up its site. Practically everything you want to know about DCP is on the Website. **PreventionPost** is even available.

The DCP site is maintained by our Webmaster, Dr. David Levin of the Biometry Research Group, who can update pages from his personal computer. Initiated four years ago, the DCP website was one of the first developed at NCI. At that time (we were part of DCPC) each Branch assumed responsibility for maintaining its section of the web. Dr. Susan Rossi helped develop many of the original homepages, including those for PLCO.

As the NCI moved forward with its web development, additional options for maintaining web pages became available. The current DCP website is a combination of pages maintained directly by individual research groups, by Dr. Levin, by Mr. Eric Graves of our Administrative Resource Center (ARC), by NCI contractors, and others. An effort is currently underway to coordinate all DCP pages to insure that they contain up-to-date information and conform to NCI web standards. The Early Detection Research Network (EDRN) has already adopted NCI standards for its site.

The web pages bring a wealth of information. They contain, for example, information about our research activities and links to key sites. Literature searches can be done through DCP's library website. Articles from on-line journals can be downloaded or books located in the library. Prevention research initiatives can be found on the Chemopreventive Agent Development Research Group's (CADRG) website. Through its site, Biometry can download programs to consumer audiences including statistical routines and data bases. The site developed by the ARC serves as a bulletin board. Questions about travel, procurement, personnel or other topics can be submitted through the site. The questions and answers are posted for all to see. Some sites even have photographs of staff, which adds a personal touch.

There are multiple links to sites critical for DCP staff. The DCP Library, for example, has links to the Library of

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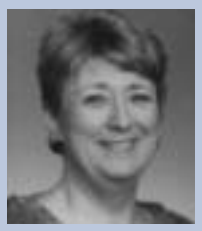
DEE SULLIVAN

We would like you to join us in welcoming new staff to DCP:

Vance Berger, PhD.
Mathematical Statistician
Biometry Research Group
From the Federal Drug Administration

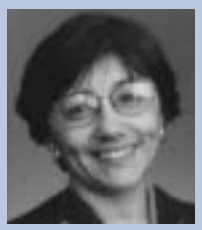


Kathleen Foster, RN
Nurse Specialist
Breast & Gynecologic Cancer Research Group
From the Lombardi Cancer Center, Georgetown University

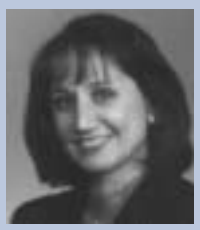
Nicholee (Nikki) Herman
Administrative Officer, ARC
From FDA

Ping Hu, ScD
Mathematical Statistician
Biometry Research Group
From the Center for Statistical Services
Brown University

Grant Izmirlian, PhD
Mathematical Statistician
Biometry Research Group
From the Epidemiology, Demographics & Biometry Program, NIA



Thea Kalebic, MD, PhD
Special Expert
Biomarkers Research Group
From the Cancer Diagnostic Program, NCI



Judith Smith, RN, MSN, AOCN
Clinical Trials Nurse Specialist
Lung and Upper Aerodigestive Cancer Research Group
From the Radiation Oncology Branch, NCI

Eva Szabo, MD
Medical Officer
Lung and Upper Aerodigestive Cancer Research Group
From the Cell & Cancer Biology Branch, NCI

Tanyan Bailey
Secretary
Nutrition Science Research Group

Linda Parreco, RN MS
Clinical Trials Nurse Specialist
Office of the Associate Director for Clinical Research

Simon Rosenfeld, PhD
Mathematical Statistician
Biometry Research Group

Departures:
Everyone at DCP sends good wishes to Lori Minasian and Julia Lawrence who recently left DCP. Lori, the former Chief of Community Oncology, joined the staff at Georgetown University. Julia was a Medical Officer in the Breast and Gynecological Oncology Research Group and is beginning a new chapter in her professional and personal life in New Orleans.

DCP Websites continued from page 10

Congress, NCI Event Calendar, National Center for Health Statistics, NIH Library, and many others. The website for CADRG contains a list of funding announcements and staff publications. The EDRN website has links to all major NCI research programs, such as the Cancer Genetics Network and the Cancer Genome Anatomy Project. The website also lists tissue and technology resources available to the extramural community through the EDRN. A list of publications by EDRN investigators is included. A link to a dietary assessment calibration/validation register is also available through the DCP website. The registry contains a search engine for publications and studies in the field of nutrition. Often, it is easier to use links to find websites than take the time with search engines to find addresses.

Plans are to make our website even more useful to DCP, the NCI, and the public. Our site will play a key role in DCP's research programs especially through secure sites. Investigators will submit research results directly through these sites enabling data to be posted rapidly. The EDRN is establishing a secure site for transmitting patient data, announcing prepublication results, and providing internal reports. Much work remains to be done on the web, but the efforts of the DCP staff are very apparent. ■

The NCI Office of Management Analysis

KAREN HARDY

The Office of Management Analysis (OMA) is the principal staff resource for management analysis at the NCI. The OMA provides several administrative related products and services that can be tailored to the needs of individual customers. These services include workload studies that provide a snapshot of resource utilization for managers; internal OMB forms; survey development and review; and records management services.

During 1999, the OMA surveyed Principal Investigators and extramural scientists to assess their satisfaction with administrative services; streamlined the OMB information collection process; and cultivated more efficient use of office space for scientific research by doubling shipments of records to the National Archives Records Center.

Marilyn G. Jackson

The OMA staff is located in EPS 330 and is ready to provide the highest quality products, services, and solutions to the NCI scientific staff. The Chief of OMA is Marilyn G. Jackson.

Information on NCI's administrative policies can be found on the OMA Website at http://www.nci.ih.gov/oma/index.htm, or call (301) 496-6985 to speak to a staff member. ■

Trials of DCP continued from page 2

more amenable to treatment and cure. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) is examining, as its name implies, the usefulness of screening modalities for each of four cancer sites: digital rectal exam (DRE) and the prostate-specific antigen (PSA) blood test for the prostate; chest x-ray for the lung; flexible sigmoidoscopy for the colorectum; and transvaginal ultrasound and the CA-125 blood test for the ovaries. PLCO randomized its first participant in 1993; enrollment will cease in 2001, after recruitment of about 150,000 participants. Individuals randomized to the intervention arm receive all applicable tests (prostate modalities are only given to men and ovarian modalities are only given to women), while individuals randomized to the control arm are asked to follow their normal health care routine. PLCO participants will be followed for at least 13 years. Completion is currently slated for 2014, but interim analyses, which may produce final results at an earlier date, will begin within a year or two.

Sometimes trials are conducted to help us identify the best way to manage disease or prevent more serious disease. The ASCUS/LSIL Triage Study (ALTS) is one such trial. ALTS is assessing how best to proceed after either of two mild abnormalities, ASCUS (atypical squamous cells of undetermined significance) or LSIL (low-grade squamous interepithelial lesions), is found on routine cervical cancer screens (Pap smears). At present, it is unclear how best to proceed when ASCUS or LSIL is diagnosed, because these lesions may resolve without treatment. Nevertheless, aggressive treatment using colposcopy is frequent in the United States because physicians cannot tell which ASCUS and LSIL lesions will regress spontaneously, which are associated with an underlying high grade lesion, and which may progress to high grade lesions. ALTS began enrollment in 1996 and finished in late 1998, randomizing about 5,000 women with ASCUS or LSIL to one of three management strategies: immediate colposcopy (cervical examination, biopsy and necessary treatment), conservative management (coloposcopy only if repeated cytology indicated a high-grade lesion), or human papilllomavirus (HPV) triage (management based in part on the results of a test for HPV, the virus believed to cause most cervical cancers). In the HPV triage arm, colposcopy was performed if cytology indicated a more severe abnormality or DNA from HPV subtypes associated with cervical cancer was present; otherwise, watchful waiting was employed. This arm was designed to assess whether an individual's HPV status is useful in determining whether colposcopy is necessary. Early results, published in this year's March 1 issue of JNCI, indicate that most women with LSIL are HPV positive. This confirms the etiologic association of HPV and LSIL, but suggests that viral testing is of limited use for triage of LSIL. The role of HPV testing in the management of women with ASCUS continues, with findings expected within the year.

Although the larger trials often receive the most attention, they are far from being the only prevention trials in DCP. Smaller studies of prevention, including chemoprevention, risk factor elimination, early detection, and disease management, are numerous. Trials in DCP have addressed smoking cessation methods, for example; others have tested pharmaceutical interventions to prevent recurrences and second primary tumors in cancer patients. Pilot studies - smaller, preliminary versions of proposed or approved studies - have been conducted to identify and correct problems before the principal study is underway. Chemoprevention trials also occur on a smaller scale, testing agents that show promise in animal or basic science research. Prevention of less common cancers is represented, too – DCP administers trials of pediatric cancer, head and neck cancer, and bladder cancer, to name a few. Precursor or early-stage lesions, including leukoplakia, colorectal adenomas, and prostate-intraepithelial neoplasia, also have been studied. ■

The Comprehensive Administrator Model–A Vision To Provide You With Better Service

JOY OSBORNE

Some of you have probably heard the DCP ARC staff talking about "Comprehensive Administrators" and a new model for providing administrative services to your program. The DCP ARC Staff would like for you to know what they are striving to accomplish.

What is a Comprehensive Administrator?

The goal of the ARC is to provide high quality administrative services to the Division of Cancer Prevention, to advance the research mission of the DCP. To help accomplish this goal, a new model for administrative employees has been conceived: the Comprehensive Administrator.

Currently, the ARC is composed of Administrative Officers, a Personnel Management Specialist, a Personnel Assistant, and Administrative Technicians. In using the Comprehensive Administrator model, the ARC will no longer have staff designated to a specific function [e.g. administration, personnel, purchasing]. Administrative services will be provided by a Comprehensive Administrator and a Comprehensive Administrative Assistant, who will address all of your needs and requests. In other words, you will be able to come to one team of administrators to handle all of your administrative needs: personnel, travel, space, budget, and so on.

This structure will increase the flexibility of the ARC staff, permitting a greater focus on the success of the DCP mission.

Pardon the Restructuring

To transform the staff into Comprehensive Administrators, the ARC developed a training plan to cross-train staff in the necessary areas. Administrative Officers are being trained in personnel areas, Personnel Management Specialists are trained in administrative areas, and support staff are cross-training each other in the necessary systems and disciplines. This training will enable the staff to assume a wider variety of duties in order to be fully functional as Comprehensive Administrators.

The ARC is also planning to add a Program Analyst to the team. The Analyst will provide essential budgetary, personnel, and systems data to the team, permitting the Comprehensive Administrators to focus on service delivery issues.

When the Comprehensive Administrators complete their training, it may be necessary to reassign some of the division's groups from the existing Administrative Officers. Your needs will be a critical part of any plan, and the ARC will consult you before any changes are put in place. You will also be notified well in advance of any changes.

How Can I Help With the Transition?

So glad you asked! Since the ARC's goal is to provide the best possible administrative services, they are developing an assessment tool to see what is currently done well, what needs improvement, and how DCP's needs are changing.

While the assessment tool is under development, it is probable that some of you will be contacted for one-on-one interviews to help refine the instrument. Once a working assessment tool is in place, the ARC will be contacting each of you. Your help in completing the assessment tool is critical–your input will plot our future course. Please give a small portion of your valuable time so the ARC can collect a substantial body of meaningful data. If you only complete two assessments this year, make it this one and the 2000 Census!

Changes and Challenges

While there are some substantial changes projected for the ARC Staff, the goal is to provide you with a seamless transition. Some challenges are ahead, the most imminent being the renovation and move within the Executive Plaza North building. Please be patient while these changes are taking place. You are valued customers, and the ARC will continue to improve its service to you! ■

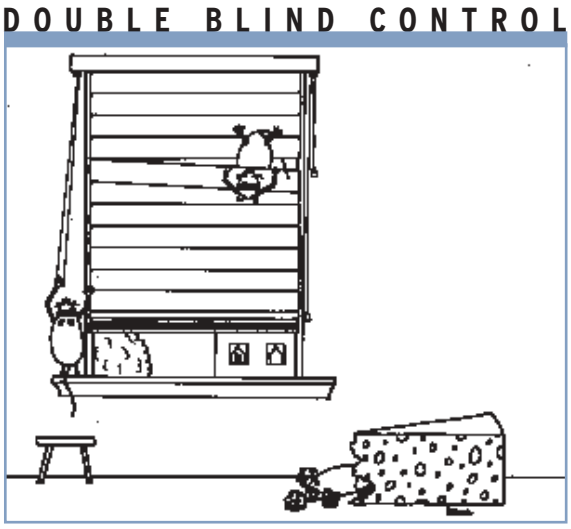


Illustration : Graça Dores

COX-2 Inhibitor continued from page 10

worsening of disease over six months in patients on placebo. This efficacy was achieved at doses where there were no differences in side effects between Celecoxib and placebo.

Background for the Trial

SCIENTIFIC

The trial is the result of an interesting combination of animal data, epidemiology studies, molecular targeting, drug discovery, and anecdotal clinical data. Scientists first observed that NSAIDS inhibit colon carcinogenesis in rodents in the mid to late 1970s. Preclinical data in the 1980s and 1990s, much from our own division, further supported this observation by demonstrating both the efficacy of many different NSAIDS, as well as efficacy of NSAIDS at later stages in the carcinogenic process. During the same time period, a number of epidemiologic studies demonstrated that regular NSAID use was associated with a significant and similar reduction in colon adenomas, colon cancers, and colon cancer related deaths in a general at-risk population. In fact, this data, along with data showing that surgical removal of adenomas profoundly reduces colon cancer risk, is perhaps the most striking data demonstrating that reduction of a preinvasive lesion (colon adenomas) profoundly affects cancer incidence. The initial anecdotal data demonstrating the efficacy of NSAIDS (Sulindac) in patients with FAP was reported by Dr. William Wadell at the University of Colorado in 1983.

The major drawback associated with the non-specific NSAIDS employed in the preclinical or epidemiologic studies is the significant amount of side effects, including stomach ulceration, which results in tens of thousands of emergency room visits and thousands of deaths per year. When most of these preclinical and epidemiologic observations were made, there was one known form of the enzyme cyclooxygenase, an enzyme that helps to metabolize arachidonic acid into prostaglandins. In 1990 it was determined that there were two forms of cyclooxygenase. The first, called COX-1, is expressed constitutively in many cells including the stomach; the second, COX-2, is expressed highly in inflammatory cells. The ability to develop specific agents that inhibit COX-2 and reduce inflammation, without effecting COX-1 and resulting in decreased side effects, had great economic potential. In fact, in a period of less than ten years, work progressed from recognition of COX-2, through development of highly specific inhibitors of COX-2, to the development of two COX-2 agents that are now on the market for arthritis and pain: Celecoxib (Searle) and Refecoxib (Merck). This provides an extraordinary example of the ability of pharmaceutical companies to develop highly specific inhibitors quickly and to bring them to market using smaller trials. Although these drugs were developed for arthritis and pain, it was found that many human tumors expressed the COX-2 isozyme. That gave immediate impetus to study its use in prevention and treatment of cancer. Results of the first small animal cancer trials with these agents were published in 1996. These studies used both a classic, chemically-induced tumor model as well as a knockout APC transgenic mouse and demonstrated striking decreases in intestinal tumors in rodents treated with COX-2 inhibitors.

NCI/Industry Collaboration

Development of partnerships between NCI and industry that will foster collaboration and potentially result in financial sponsorship of prevention trial is not trivial. One of the major concerns for industry is the possibility that a prevention trial will take ten or more years to complete, while a therapy trial takes one to two years. As of the mid 1990s, a number of drug companies were developing COX-2 inhibitors. The Chemoprevention Branch, under the direction of Dr. Gary Kelloff, had ongoing interactions with several pharmaceutical companies. The company with the greatest interest in a COX-2 inhibitor was Searle. Phil Needleman, one of the pioneers in COX research, and John Alexander both had a potential COX-2 selective inhibitor and an interest in the possibilities of prevention studies. The addition of two individuals who were highly committed to the development and completion of the trial, Ernest Hawk and Gary Gordon, significantly enhanced these efforts. Ernest Hawk, whose primary interest is in GI cancers, was in DCP's Chemoprevention Branch, and Gary Gordon, a researcher from Johns Hopkins, joined Searle. This NCI/industry interaction certainly facilitated completion of a small-scale prevention trial, and was particularly helpful in the instance of novel drugs. An important aspect of accomplishing the study was the use of a trial design that would give a strong indication of efficacy within a few years, a major objective for all further Phase II trials. It is probably one of the more striking examples of using genetically-defined cohorts in a prevention trial.

Implications for Patients with FAP

The FDA determined that the results of the clinical trial, in conjunction with data in Minmice (the mouse genetic equivalent of FAP) that showed striking efficacy of Celecoxib, warranted the recommendation that Celecoxib be given for adults with FAP to complement their standard care, which consists of prophylactic surgery and endoscopic surveillance. What is the potential use of this agent for individuals with FAP? The vast numbers of adenomas associated with FAP result in repeated surgeries for affected individuals. Furthermore, FAP patients will ultimately develop invasive cancer as well. The use of an effective agent in this context may 1) facilitate endoscopic exams by reducing adenoma numbers, 2) delay or pre-

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COX-2 Inhibitor continued from page 14

vent GI surgery, 3) delay or prevent disease emergence in adolescents, and 4) reduce or delay duodenal neoplasia.

Mechanisms Large-Mechanisms Small

Celecoxib is a highly selective COX-2 inhibitor and a superb example of molecular targeting. There is little doubt that its effect on arthritis is related to alterations in prostaglandin levels that result in profound alterations in the inflammatory reaction. How COX-2 influences tumor cells may be less obvious. Is the apoptosis observed in many tumor cells following COX-2 treatment directly related to alterations in prostaglandins and arachidonic acid metabolism (ceramide) or are there other effects, such as direct effects on PPAR receptor? Must COX-2 be observed in tumor epithelial cells of specific organs to be a candidate for a study? Or does its presence in stroma, infiltrating macrophages, or even new vascular cells connote a sufficient target? The latter might imply that COX-2 is a relatively effective anti-angiogenic agent about which there is already significant clinical data. We have found Celecoxib to be effective in a UV skin model where COX-2 is highly expressed in tumor epithelial cells, in mouse intestinal adenomas (Min) where it appears to be expressed in the stroma and macrophages, and in mouse bladder cancer where it appears to be expressed primarily in endothelial cells.

What Is To Be Done

Based on the data collected in the FAP trial, a number of additional studies could be performed in these patients: 1) suppression or delay of multiple adenomas in adolescents with FAP; 2) confirmation of effects in longer term trials; and 3) potential studies combining COX-2 with other effective agents (e.g., DFMO) to enhance efficacy. Furthermore, since mutations in the APC gene are associated not only with the FAP syndrome but also with most sporadic colon polyps and colon cancers, prevention trials in this area seem obvious. The striking animal data and COX-2 staining in human actinic keratoses and bladder tumors also makes these trials obvious. COX-2 is over-expressed in many human cancers including lung, esophagus, breast, and pancreas and therefore may be a logical agent to be tested in prevention trials. If the anti-antigenic theory is correct, the opportunities seem limitless for COX-2. In the end only intelligent and timely clinical trials will determine its efficacy. Is its usefulness limited to FAP or is it useful for the colon or perhaps the entire GI tract? Is it more generally applicable, perhaps the ultimate cancer panacea? One way or the other, the COX-2 inhibitors have had a promising start and there is certainly more to come. ■

Project Teams continued from page 4

Prevention of Languishing Studies (POLS)

NCI medical officers are acutely aware that clinical trials languish for any of a number of reasons, including: cohort and agent unavailability, staff issues, regulatory hurdles, legal negotiations, and pharmaceutical industry priorities. The POLS Project Team was formed to identify salient features of languishing Phase II and III clinical trials and it presented an interim report to the Coordinating Unit (CU) in March 2000. The team concluded that in the majority of cases, poor accrual and failure to acquire agents is common in languishing studies. Although less common, staff issues (at the NCI and/or study sites) may be associated with study delays.

In an effort to increase efficiency of trial execution, POLS created schedules based on completed or current studies to serve as performance measures for DCP-contracted and CCOP clinical trials. POLS intends to use these measures to identify studies at risk for falling short of completion, optimize potential for rescuing high risk studies, and reduce obstacles for other Division studies. The team recruited a working group for the second phase of this effort, assisting studies behind schedule. The working group will set up a preliminary internal review to identify interventions that the NCI might initiate or suggest to the investigators, then monitor efficacy of these interventions. "The Division is hopeful that early intervention for studies at risk for delayed or failed execution will translate into fewer wasted resources or missed opportunities to answer important scientific questions in clinical trials for cancer prevention," said Jaye Viner, team co-leader. Rose Mary Padberg is the other co-leader. Members of NCI contracts branch and the DCP support contractor, CCS Associates, also participate on the team.

Single Nucleotide Polymorphism (SNP)

The SNP project team is exploring the functional significance of genetic polymorphisms in terms of both gene-gene and gene-environment interactions. "The SNPs analysis of relevant genes will be used as a molecular tool to explore the genetic basis of cancer susceptibility and/or drug response in clinical trials," explained Iqbal Ali, the team leader. Currently, the team is developing a study that will identify and evaluate SNPs in patients at increased risk for colon cancer due to Familial Adenomatous Polyposis who respond to a certain chemopreventive agent.

The project team is the nucleus of a matrix-based organization. The number, type, and composition of project teams tell a lot about the values, priorities, and goals of an organization. As DCP fills the blank "eggs" on the organization chart, we will see what our project teams say about us. ■

The Rise and Fall of the Clinical Trial Paradigm

DOUGLAS L. WEED
Editor-in-Chief

My family congregates at North Carolina's Outer Banks every other summer for a week of freshly caught shrimp at vacation prices and ocean swimming. Traditionally, our first activity is to jump in the surf. Later, we walk the beach from pier to pier. Along the way we marvel at the size and splendor of new cottages perched on giant wooden posts and wonder how many years it will be before the sea obliterates their protective dunes and swallows them whole. Two very different forces are at work: the slow but steady erosion of wind and tide-bound surf, and second, the mighty storms that can steal ten feet of dune in an afternoon.

Remarkably similar forces endanger the methods and theories of biomedical science. Ask any historian or philosopher of science. They will tell you about the slow but steady evolution of scientific thought, the erosion of ignorance if you will, as our understanding of disease mechanisms, etiology, and prevention gradually increases with each published paper or technical report. They will also tell you about the occasional upheaval in thought, the scientific revolution, that transforms theories and methods in a historic instant. Physical sciences were the first carefully studied examples of this view—the paradigm view—most often associated with Thomas Kuhn, a philosopher-historian. But earlier thinkers, such as Ludwig Fleck, wrote about the same phenomena in medical science. Today, this view is very popular and there are many examples of revolutionary discoveries and paradigm shifts: X-rays, DNA, and the causal effects of tobacco, to name a few. Methodologic examples abound: applying quantitation to medicine and, as you may have guessed, the method featured in this issue of **PreventionPOST:** the randomized clinical trial, dominating scientific methodology in medicine for the past fifty years.

The paradigm view of biomedical science, in which periods of evolution are punctuated by occasional revolutions, implies that whatever we think we know today—whether theory of cancer causation or method of evaluation—will eventually be overthrown, altered significantly, revolutionized. Someday, someone's brain will light up like Tom Terrific's and, in an instant, a sizable chunk of what we think we know will become obsolete.

If all of this sounds a bit abstract and a little too much like the science fiction novels that make summertime beach reading a joy, consider the fact that nearly everyone accepts the randomized clinical trial as the strongest possible way to test a hypothesis. Randomized trials sit at the top of everyone's list of evidentiary hierarchies. After all, what could possibly be better than the results of a randomized controlled clinical trial? What could possibly be a stronger, more valid, way to test the efficacy of interventions?

I don't have an answer and I don't know when someone will. But if I were a gambling man, I'd bet that eventually the rise and fall of the randomized trial paradigm will be taught in courses on the history of medicine and public health. Then again, if I were a gambling man, I'd go to Atlantic City for my summer vacation and get free shrimp. ■

PreventionPOST
Newsletter of the Division of Cancer Prevention
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